TITLE OF THE INVENTION

SEMISOLID MATRIX PHARMACEUTICAL FORMULATIONS

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to pharmaceutical formulations with improved stability comprising at least one oxidation-susceptible and poorly water-soluble drug as active ingredient and a water soluble derivative of vitamin E as antioxidant agent.

Discussion of the Background

Solid dispersions cover a wide range of systems comprising one or more active ingredients in an inert pharmaceutical carrier or matrix in the solid or semisolid state as established by Chiou and Riegelman (Journal of Pharmaceutical Sciences 1971, 60(9); 1291-1302).

The authors report several solid dispersion manufacturing methods including melting method, solvent method and melting-solvent one.

Solid dispersions represent a useful pharmaceutical technique for increasing and modifying the dissolution kinetics of poorly soluble drugs to improve their oral bioavailability. Hydrophilic and highly soluble polymers have been widely investigated as inert carriers in solid dispersions for accelerating release profiles of poorly water-soluble drugs.

Always Chiou and Riegelman refer that water-soluble crystalline polymers of high molecular weight appear to be the preferred solid dispersion carriers for sparingly water soluble drugs, since the molecular weight of the most organic drug is usually less than 1000. Low toxicity and lack of absorption from the gastrointestinal tract are the important advantages of these polymeric carriers.

Polyvinyl pyrrolidone (PVP) and polyethylene glycols (PEG) of high molecular weight are the most frequently investigated polymeric carriers, although thermal decomposition

of PVP makes not applicable the use of melting method and makes this polymer less attractive in formulation than PEGs.

Lheritier et al. (International Journal of Pharmaceutics 123, (1995) 273-279) refer the improved dissolution behavior of a new calcium family compound by means of solid dispersions containing PEG 6000.

It is well known to the man skilled in the art that the poor water solubility of drugs could affect their oral administration and absorption. When poor water solubility is associated with poor chemical stability properties due to oxidative reaction under stressed conditions (for example heat, moisture and light) the bioavailability of oral formulations of the drug could further decrease.

This oxidative reaction happens in common oral dosage forms such as uncoated tablets, powders, fine granules, hard gelatin capsules; thus the content decreases and visual aspect alteration (for example color changes) can occur either during the manufacturing process and storage, that can be overcome through sugar coated film coated.

Non conventional oral dosage forms can overcome and increase the low water solubility of compounds thus impacting not only on the stability but also on the dissolution properties, the oral absorption and bioavailability of the active ingredient.

However, in case of oxidation-susceptible drugs a hydrophilic carrier based solid dispersion is not the preferred choice for the formulation skilled in the art; especially high molecular PEGs, according to their high solubilization properties, can undergo autoxidation reactions during the storage catalyzing both its and the drug degradation.

Traditional formulation skills and knowledge may suggest selection of appropriate stabilizing agents for overcoming oxidation degradations and improving chemical stability.

The most relevant selection criteria is miscibility of the stabilizing agent with hydrophilic carriers and good stability during the solid dispersion manufacturing process that is usually carried out by melting method at 50-70°C.

In some cases improved stability effects have been obtained adding stabilizing agents that can at the same time adversely affect the dissolution properties of the solid dispersion formulations.

Conventional antioxidant agents such as ascorbic acid, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate (PG) and the like have been shown to be not compatible for PEGs based solid dispersions either due to physical incompatibility and chemical degradations.

Surprisingly a stability improvement has been obtained by adding a low amount of a water soluble vitamin E derivative, in particular vitamin E polyethylene glycol succinate (Vitamin E TPGS) in the solid dispersion composition.

Vitamin E TPGS (Eastman) is a water miscible d-⇔tocopheryl derivate obtained by esterification of the acid group of crystalline d-⇔tocopheryl acid succinate by polyethylene glycol (see U.S.Pharmacopeia 25 – National Formulary 20); having a dual nature of lipophilicity and hydrophilicity, similar to a surface active agent.

Vitamin E TPGS is already known as a pharmaceutical antioxidant active ingredient for treatment human diseases. For example, US 6,069,167 discloses the use of this water-soluble derivative of Vitamin E to treat cholestatic liver disease, and US 5,972,993 discloses the use of tocopherol derivatives such as vitamin E TPGS for the treatment of skin disorders.

However, its use in pharmaceutical applications as excipients is as emulsifier, solubilizer, and absorption enhancer. WO 96/36316, US 5,891,845 and WO 00/76482 may be cited as examples.

WO 00/03753 discloses the use of Vitamin E TPGS as a component of microdisperse drug delivery system for enhancing the bioavailability of therapeutics agents; in this case Vitamin E TPGS acts as a semisolid carrier in mixture with polyglycolyzed glycerides to produce a solid, semi-solid or liquid dosage form.

WO 01/37834 describes a stable oral pharmaceutical dosage form containing an acid benzimidazole compound mixed with pharmaceutical acceptable excipients including vegetable and/or animals oils, and/or synthetic triglycerides. The preferred stabilizing agent is Vitamin E TPGS added for improving chemical stability of labile acids active ingredient but in this case the stabilization effect is not linked to oxidation but to liability to acid of said molecules.

We have found that unexpected improvements in chemical stability of oxidation-susceptible and poorly water-soluble drugs formulated in a hydrophilic carrier based solid

dispersion can be obtained by adding low amount of vitamin E TPGS as antioxidant agent.

DETAILED DESCRIPTION OF THE INVENTION

Object of the present invention is a stable pharmaceutical solid or semisolid dispersion comprising at least one oxidation-susceptible and poorly water-soluble drug as active ingredient, a hydrophilic carrier, a water-soluble vitamin E derivative as antioxidant agent and optionally other excipients.

Another object of the invention is a method of inhibiting oxidative degradation of pharmaceutical formulations containing at least one oxidation-susceptible and poorly water-soluble drug as active ingredient which method comprises adding to the formulation a low amount of a water soluble vitamin E derivative as antioxidant.

A further object of the invention is a simple, quick and cheap manufacturing process for preparing a stable solid or semisolid dispersion for oral administration of an oxidation-susceptible and poorly water-soluble drug which process comprises mixing the oxidation-susceptible and poorly water-soluble drug, the hydrophilic carrier and the water soluble vitamin E derivative, and melting the resultant mixture.

Although a broad number of oxidation-susceptible and poorly water-soluble drugs could benefit from the improved stability provided by the present invention, active ingredients incorporating at least one amine, aldheyde or hydroxy functional group or having at least a double or triple bond in their chemical structure and having an intrinsic solubility in water of less than about 500 ¢g/mL, especially less of about 200 ¢g/mL are preferred.

Specific examples of active ingredients which can be used in the present invention are posaconazole, tocoretinate, nitrendipine, tiagabine, hydrocortisone/cortisol, tacrolimus, testosterone, metaclazepam, morphine, metamethasone valerate, captopril, nicotine, dronabinol, formestane, atamestane and exemestane.

Exemestane is the most preferred oxidation-susceptible and poorly water-soluble drug according to the present invention.

In fact, exemestane is an irreversible aromatase inactivator that works on the aromatase enzyme inhibiting the conversion of androgens to estrogens. This compound has low water solubility, about 70 ¢g/mL, that could affect the oral administration and absorption of this active drug. Besides exemestane exhibits poor chemical stability properties due to oxidative reaction under stressed conditions.

The drug can be dispersed in the pharmaceutical solid dispersion in the range of from about 25% to 1% and more preferably from 15% to 2%.

The pharmaceutical composition of this invention further comprises a hydrophilic carrier, a water soluble vitamin E derivative as antioxidant and optionaly further excipients.

Hydrophilic polymers are added as inert carrier of the solid dispersion to improve the dissolution release profile and the solubilization of the active drug from the pharmaceutical dosage form.

Examples of hydrophilic carriers are high molecular weight polyethylene glycols such as PEG 1000, 2000, 3000, 4000, 6000, 8000 and 20,000.

Hydrophilic carriers can be in an amount from 20% to 95% w/w and preferably from 90% to 70% w/w.

The antioxidant agent is water soluble vitamin E derivative, preferably d-alpha-tocopherol polyethylene glycol ester, and more preferably d-alpha-tocopherol polyethylene glycol 1000 succinate, also known as vitamin E TPGS.

The water-soluble vitamin E derivative is used in the range from 1% to 0.01% w/w of the pharmaceutical composition, and preferably from 0.5% to 0.02% w/w.

Other suitable excipients which can be optionally added to the pharmaceutical composition of the invention are surface active agents for improving the dissolution of the active drug from the solid dispersion filled in capsules.

They may comprise polysorbates (for example Tween 80) and/or pluronics in the range from 20% to 0.5 % w/w and preferably from 5 % to 1 % w/w of the pharmaceutical composition.

The preferred manufacturing process is mixing the oxidation-susceptible and poorly water-soluble drug, the hydrophilic carrier and the water soluble vitamin E derivative, then optionally adding one or more other pharmaceutical components and melting the final mixture at temperatures between 50°C and 70°C.

The melt solid dispersions are mixed from several hours up to 48 hours. Final dosage forms are hard gelatin capsules (HGC), soft gelatin capsules (SGC) or hydroxypropylmethyl cellulose capsules (HPMC) prepared by direct filling of the molten excipients with the active drug.

With the aim of better illustrating the present invention, without limiting to it, the following examples are now given.

Example 1

Solid dispersion of exemestane in PEG 4000.

5 mL of PEG 4000 were melted at 70°C and 750 mg of exemestane were dispersed under magnetic stirrer. After 4, 24 and 48 hours at 60°C, "4" size hard gelatin capsules were manually filled with 0.160 mL of molted dispersion and correlates assay is performed by means HPLC method.

The accepted limit content of the known degradation exemestane compounds is the following:

Related substance "A": less than 1%

Related substance "B": less than 0.5%

The results on the said composition are the following:

Area %	After 4h	After 24h	After 48h
Related substance "A"	0.62	0.57	1.03
Related substance "B"	0.86	0.95	1.26

Example 2

A solid dispersion having the following composition:

PEG 4000	88.5 %	(w/w)
exemestane	11%	(w/w)
propyl gallate	0.5 %	(w/w)

was prepared by the melting method described in Example 1.

After 48 hours sensitive change in solid dispersion color, from white to brown, were observed due a chemical instability of propyl gallate at high temperatures.

Example 3

Solid dispersions having the following composition:

PEG 4000	87.3 %	(w/w)
exemestane	12.7%	(w/w)

were prepared by the melting method described in Example 1, adding respectively 0.2% w/w, 0.02% w/w of butylated hydroxyanisole (BHT) or butylated hydroxytoluene (BHT).

After 4, 24 and 48 hours at 60°C, "4" size hard gelatin capsules were manually filled with 0.160 mL of molted dispersion and correlates assay is performed by means HPLC method.

The results of all compositions are the following:

Area %	After 4h	After 24h	After 48h
Related substance "A"	0	0	0
Related substance "B"	0	0	0

Nevertheless after 48 hours dramatic decrease of dissolution profiles were observed in comparison to pharmaceutical composition described in Example 1 probably due to physical incompatibility between PEG and these phenol derivatives (see Figure 1 and 2).

Example 4

A solid dispersion having the following composition:

PEG 4000	87.3 %	(w/w)
exemestane	12.5%	(w/w)
Vitamin E TPGS	0.2 %	(w/w)

was prepared by the melting method described in Example 1.

After 4, 24 and 48 hours at 60°C, "4" size hard gelatin capsules were manually filled with 0.160 mL of molted dispersion and correlates assay is performed by means HPLC method.

The results on the said composition are the following:

Area %	After 4h	After 24h	After 48h
Related substance "A"	0	0	0
Related substance "B"	0	0	0

No solid dispersion color changes were observed among the manufacturing process.

Example 5

A solid dispersion having the following composition:

PEG 4000	87.48 %	(w/w)
exemestane	12.5%	(w/w)
Vitamin E TPGS	0. 02 %	(w/w)

was prepared by the melting method described in Example 1.

After 4, 24 and 48 hours at 60°C, "4" size hard gelatin capsules were manually filled with 0.160 mL of molted dispersion and correlates assay is performed by means HPLC method.

The results on the said composition are the following:

Area %	After 4h	After 24h	After 48h
Related substance "A"	0	0	0
Related substance "B"	0	0	0

No solid dispersion color changes were observed among the manufacturing process.

Example 6

A solid dispersion having the following composition:

PEG 4000	86.8 %	(w/w)
Exemestane	10 %	(w/w)
Vitamin E TPGS	0.2 %	(w/w)
Tween 80	3 %	(w/w)

was prepared by the melting method described in Example 1.

After 48 hours at 60°C, "2" size hard gelatin capsules were manually filled with 0.247 mL of molted dispersion.

These capsules were stored at 55°C, 25°C/60% HR and 40°C/75% HR according to the following stability protocol:

Conditions	Timepoints				
	T0	15 days	1 month	3 months	6 months
55°C	A	A	A		
40°C-75%HR	A		A	A	A
25°C-60%HR	A			A	A

A- Assay and correlates

The results are the following:

	T 0	15 days at 55°C	1 m at 55°C	1 m at 40°C / 75% RH	3 m at 40°C / 5% RH	3 m at 25°C / 60% RH	6 m at 40°C / 75% RH	6 m at 25°C / 60% RH
	Assay	Assay	Assay	Assay	Assay	Assay	Assay	Assay
Assay	102.64%	102.64%	104.87%	103.16%	100.79%	103.14%	101.41%	101.15%
Related substance "A"	0%	0%	0%	0%	0%	0%	0%	0%
Related substance "B"	0%	0%	0%	0%	0%	0%	0%	0%